REMARKS

I. Status Summary

The present U.S. patent application is a divisional of U.S. Patent 6,270,758, filed October 8, 1998. Claims 64-84 are currently pending in the present application.

Claims 64-84 have been rejected under 35 U.S.C. § 103(a) upon the contention that the claims are obvious over Gao *et al.*, 1995 (*Vaccine* 13(9):871-877; hereinafter referred to as "Gao") in view of Elson *et al.*, 1996 ("Cholera Toxin as a Mucosal Adjuvant", in Mucosal Vaccines 59-72 (Academic Press; hereinafter referred to as "Elson"). Claims 64-84 have also been rejected under this section upon the contention that the claims are obvious over Abraham *et al.*, 1992 (*J. Immunol.* 149:3719-3726; hereinafter referred to as "Abraham") in view of Elson. The bases for these rejections can be found in the Official Action dated March 17, 2004 on pages 2-4.

Reconsideration of the application as amended and based on the remarks set forth herein below is respectfully requested.

II. Responses to the Rejections under 35 U.S.C. § 103(a)

II.A. Response to the Rejection over Gao in view of Elson

Claims 64-84 have been rejection under 35 U.S.C. § 103(a) upon the contention that the claims are obvious over Gao in view of Elson. According to the United States Patent and Trademark Office (hereinafter "the Patent Office"), Gao teaches a method of eliciting both a mucosal and systemic immune response in a mammal by intramucosal administration of IL-1β. Gao is also asserted to teach that the antigen and adjuvant are not conjugated together, and that the composition is free of mineral adjuvants, preservatives, or stabilizers, and is in a pharmaceutical composition (see Official Action at pages 2-3). The Patent Office also asserts that Gao showed that subcutaneous administration of bovine herpesvirus-1 envelope glycoprotein I (gI) and IL-1β induced strong mucosal as well as systemic antibody response. The Patent Office concedes, however, that Gao does not teach mucosal administration of an antigen together with an

adjuvant, the use of IL-1α, IL-12, IL-15, or IL-18, the recited dosing range and schedule, the administration of these interleukins with other cytokines, the recited vehicles (including PBS), or use of this composition in humans.

The Patent Office asserts that these deficiencies are cured by Elson, which is asserted to teach that many pathogens invade or cause disease at mucosal surfaces and that mucosal administration has the distinct advantage of being an easy route of administration that can induce both systemic and mucosal immune responses. The Patent Office thus asserts that it would have been obvious to one of ordinary skill in the art at the time the invention was made to (a) modify the administration method of Gao by administering antigen-adjuvant compositions intramucosally because Elson teaches that this route induces both systemic and mucosal immune responses; (b) adjust both the dose and the administration schedule to maximize the effect of the administered composition; (c) to administer the composition to humans since Gao taught that the composition was safe and effective in calves; (d) use PBS as a vehicle since it is a safe and widely used vehicle; and (e) use any interleukin (for example IL-1α, IL-12, IL-15, and/or IL-18) with or without cytokines because Gao taught that IL-1β was effective and it would be expected that if IL-1β was effective any other interleukin would be effective since the family of compounds and administration technique is the same.

After careful consideration of the rejection and the Patent Office's bases therefor, applicants respectfully traverse the rejection and submit the following remarks.

Applicants respectfully submit that in order to meet its burden in establishing a prima facie case of obviousness, the Patent Office must show that the cited references disclose or suggest all claim elements, and that there is a motivation or suggestion to combine the teachings of the references to arrive at the claimed invention with a reasonable expectation of success. Furthermore, the claimed invention must be considered as a whole; each reference must also be considered as a whole and suggest the desirability and thus obviousness of making the combination; the references must be reviewed without benefit of hindsight vision afforded by the claimed

invention; and "ought to be tried" is not the standard with which obviousness is determined. See M.P.E.P. §§ 2142-2144.

Initially, applicants respectfully traverse the Patent Office's contention that Gao teaches eliciting both a mucosal and systemic immune response in a mammal by administering IL-1β via an intramucosal route. Applicants respectfully submit that close inspection of Gao clearly demonstrates that the animals in Gao were immunized subcutaneously at the base of the ear. Applicants respectfully submit that this is not an intramucosal route of administration. Although the Patent Office appears to concede that this reference does not teach mucosal administration, applicants wish to point out that the Patent Office's assertion that Gao administered IL-1β via an intramucosal route is inaccurate.

Thus, at best Gao discloses that subcutaneous administration of an antigen in the presence of IL-1β and incomplete Freund's adjuvant can give rise to an immune response. The reference does not disclose or suggest that the same composition would have elicited an immune response if administered intramucosally, or even if the composition lacking incomplete Freund's adjuvant (i.e. antigen plus IL-1β alone) would be capable of eliciting an immune response at all. Thus, even assuming arguendo that Gao teaches that IL-1β had some effect on the immune response that was seen, it does not demonstrate that gl plus IL-1β alone would have elicited any immune response whatsoever. Given the art-recognized adjuvant ability of Incomplete Freund's adjuvant, applicants respectfully submit that it cannot be concluded from Gao that antigen plus IL-1β (or any cytokine, for that matter) would be capable of eliciting an immune response when administered intramucosally. Claim 64, on the contrary, specifically recites that the antigen-adjuvant composition is administered intramucosally, and that initial contact occurs in mucosal tissue of the vertebrate subject to elicit an immune response. Applicants respectfully submit that this element is not disclosed or suggested in Gao.

Furthermore, claim 64 recites that the cytokine adjuvant is selected from the group consisting of IL-1α, IL-12, IL-15, IL-18, and combinations thereof. Applicants respectfully submit that these elements are also not disclosed or suggested by Gao.

Thus, no motivation can be derived from Gao for intramucosal administration of an antigen-adjuvant composition comprising the antigen and a cytokine adjuvant selected from the group consisting of IL-1α, IL-12, IL-15, IL-18, and combinations thereof to produce an immune response.

The Patent Office asserts that the deficiencies of Gao are cured by Elson. Applicants respectfully disagree. Elson's teachings are limited to the assertions that living pathogens are capable of invading and/or causing disease at mucosal surfaces and that mucosal administration can induce both systematic and mucosal immune responses against such pathogens. Thus, Elson does not provide any suggestion that intramucosal administration of antigen-adjuvant compositions will give rise to an immune response. Additionally, Elson does not disclose the use of cytokine adjuvants comprising IL-1α, IL-12, IL-15, IL-18, and combinations thereof, another element of claim 64. Accordingly, applicants respectfully submit that that neither Gao nor Elson disclose these elements, and thus do not together support a prima facie case of obviousness of the rejected claims.

Furthermore, the entireties of the Gao and Elson references must be taken in context, and applicants respectfully submit that when the teachings of the references are taken as a whole, one of ordinary skill in the art would not have been motivated to attempt to use antigen-cytokine adjuvant compositions to elicit an immune response to the antigen by intramucosal administration. More particularly, Gao discloses that "the mucosal immune response to most soluble antigens administered directly to the mucosal system is low and requires a large amount of antigen and frequent vaccinations" see Abstract. As a result, the authors attempted to generate a mucosal immune response by subcutaneous injection of a combination of antigen, IL-1β, and incomplete Freund's adjuvant at a site that shares lymphatic drainage with the nasal mucosa in order to prime mucosal immunity. Thus, it appears that the reason that this strategy was chosen over the assertedly "easy method" of Elson is that the authors did not believe that administering IL-1β and the antigen intramucosally would produce an immune response.

Additionally, those of skill in the art appeared to share the belief that enzymatic activity in the mucosa presented an insurmountable barrier to the effective use of cytokine adjuvants for intramucosal delivery of antigens. Recognizing this, Kramer *et al.* (Item C12 of IDS filed June 5, 2001) specifically stated that for intramucosal delivery of soluble cytokines, "it will be necessary to develop strategies to chaperone these materials to the mucosa by incorporation into delivery vehicles which ensure that they reach the mucosal epithelium in intact form and which maximize uptake across the mucosal epithelium" (Kramer *et al.* at page 393; emphasis added). Thus, applicants respectfully submit that it is only with reference to the instant specification that one of ordinary skill in the art would have been motivated to attempt intramucosal delivery with the claimed compositions. Therefore, it is respectfully submitted that no motivation to combine the references under 35 U.S.C. § 103(a) can be found within the references themselves.

The Patent Office also asserts that since it would be expected that, if IL-1β is effective in the method of Gao, then any other interleukin would also be effective. Applicants respectfully submit that this assertion is not supported by any scientific evidence, nor by any teachings in the cited combination. Additionally, this assertion, even if it were true, assumes that the administration technique disclosed in Gao is the same as claimed in the instant application as asserted by the Patent Office. With reference to the discussion presented hereinabove, it is clear that the administration technique disclosed in Gao is not the same as claimed in the instant method, as Gao used subcutaneous administration and the instant claims recite intramucosal administration.

Furthermore, Elson specifically teaches away from the instant invention by stating "most protein antigens are not only poor immunogens when given mucosally, but induce tolerance instead of immunity" (emphasis added). Thus, irrespective of the ease of mucosal administration, Elson suggests that intramucosal administration with protein antigens would be expected to induce tolerance, instead of eliciting an immune response.

When taken together and in their entireties, applicants respectfully submit that both Gao and Elson teach away from the claimed invention by disclosing essentially that direct deposition of antigens onto a mucosal surface of a vertebrate would not be expected to elicit an immune response, and may in fact tolerize the vertebrate to the antigen. As a result, applicants respectfully submit that no motivation to combine the references as proposed by the Patent Office can be found, and further that the references do not provide a reasonable expectation of success in arriving at the claimed invention. Furthermore, applicants respectfully submit that the only way that these two references can be combined is with hindsight reference to the instant specification.

Accordingly, applicants respectfully submit that the Patent Office has not met its burden in presenting a prima facie case of obviousness of claim 64 over Gao in view of Elson. Claims 65-84 depend directly or indirectly from claim 64, and are thus also believed to have been patentably distinguished over the cited references. Applicants respectfully request that the instant rejection of claims 64-84 be withdrawn. Allowance of claims 64-84 is also respectfully requested.

II.B. Response to the Rejection over Abraham in view of Elson

Claims 64-84 have also been rejected under 35 U.S.C. § 103(a) over Abraham in view of Elson. According to the Patent Office, Abraham teaches that intranasal administration of bacterial polysaccharide and IL-2 resulted in an increased bacterial-specific pulmonary immunity and pulmonary plasma cells. The Patent Office concedes, however, that Abraham does not teach the use of IL-1α, IL-12, IL-15, or IL-18, the recited dosing range and schedule, the administration of these interleukins with other cytokines, the recited vehicles, or the use in humans. The Patent Office asserts that these deficiencies are cured by Elson for the reasons set forth hereinabove with regard to the previous rejection.

After careful consideration of the rejection and the Patent Office's bases therefor, applicants respectfully traverse the rejection and submit the following remarks.

Initially, applicants respectfully direct the Patent Office's attention to the discussion above regarding the Elson reference. The Patent Office concedes that Abraham does not teach the use of IL-1α, IL-12, IL-15, or IL-18, the recited dosing range and schedule, the administration of these interleukins with other cytokines, the recited vehicles (including PBS), or use of this composition in humans. For the reasons set forth hereinabove, applicants respectfully submit that Elson does not cure this deficiency in Abraham, and thus the combined references do not disclose or suggest each and every element of claim 64.

The Patent Office asserts that Abraham discloses the use of IL-2, and thus that it would be obvious to have used any interleukins with and without cytokines since "it would be expected that, if IL-2 is effective in the method of Abraham, then the use of any interleukin, including IL-1α, IL-12, IL-15, and IL-18 would also be effective since the family of compounds and administration technique is the same". Official Action at page 4. For the same reasons as discussed hereinabove for the Gao reference, applicants respectfully traverse this assertion as based on no scientific support and finding no support in the cited references themselves. Furthermore, these cytokines are known to be produced by different cells and to act on different targets. IL-2, for example, is produced mainly by T4 lymphocytes, whereas IL-1α, IL-12, IL-15, and IL-18 are produced mainly by monocytes, macrophages, and dendritic cells. Thus, applicants respectfully submit it is only by viewing the cited references with hindsight vision to the instant specification that the Patent Office has grouped IL-2 with IL-1α, IL-12, IL-15, and IL-18 for the formulation of an adjuvant.

Summarily, applicants respectfully submit that contrary to the Patent Office's contention, one of ordinary skill in the art would not have been motivated to replace the IL-2 of Abraham with any or all of IL-1α, IL-12, IL-15, and/or IL-18. As such, applicants respectfully submit that no reasonable expectation of success can be found for substituting the IL-2 of Abraham with any of the claimed cytokines to produce an antigen-adjuvant composition for eliciting an immune response by intramucosal administration.

Accordingly, applicants respectfully submit that the Patent Office has not presented a prima facie case of obviousness of claim 64 over Abraham in view of Elson. Claims 65-84 depend directly or indirectly from claim 64, and are thus also believed to have been patentably distinguished over the cited references. Applicants thus respectfully request that the rejection of claims 64-84 under 35 U.S.C. § 103(a) over Abraham in view of Elson be withdrawn. Applicants further submit that the claims are in condition for allowance, and respectfully solicit a Notice of Allowance to that effect.

CONCLUSIONS

In light of the above amendments and remarks, applicants submit that the application is in condition for allowance and courteously solicit a Notice of Allowance.

If any small matter should remain outstanding after the Patent Examiner has had an opportunity to review the above Remarks, the Patent Examiner is respectfully requested to telephone the undersigned patent attorney in order to resolve these matters and avoid the issuance of another Official Action.

DEPOSIT ACCOUNT

The Commissioner is hereby authorized to charge any deficiencies of payment or credit any overpayments associated with the filing of this correspondence to Deposit Account No. **50-0426**.

Respectfully submitted,
JENKINS, WILSON & TAYLOR, P.A.

Date: 06/17/2004 By: Arles A. Taylor Jr.

Arles A. Taylor, Jr.
Registration No. 39,395

180/102/2 AAT/CPP/ptw

Customer No.: 25297